Subject Category: The Effect of Chronic Air Pollutant and Aeroallergen Exposures on Asthma in Children

I.a. **Core Hypotheses:**

- After adjusting for potential confounders, the incidence of asthma in children is positively associated with chronic exposures to air pollutants, such as PM, ozone, PAHs, volatile organic compounds, and other criteria and toxic air pollutants.

- After adjusting for potential confounders, the incidence of asthma in children is positively associated with chronic exposures to endotoxin, dust mites, cockroach, and other allergens.

- After adjusting for potential confounders, the incidence of asthma in children is positively associated with chronic exposures to pollen, fungi, and other outdoor aeroallergens.

I.b. **Sub-Hypotheses: Chronic Exposure Estimation**

- Long-term air pollutant exposures of children can be estimated using GIS, non-parametric regression and geographic smoothing techniques together with residential histories and publicly accessible data, including those from EPA's Aerometric Information Retrieval System (AIRS), the National Weather Service, the U.S. Census, and the Emissions Inventory Database.

- Long-term exposures to dust mite, cockroach, and other allergens for a child can be estimated from annual sampling of current home allergen levels, housing questionnaire responses, and allergen-specific T cell counts.

- Long-term exposures to outdoor allergens, such as fungi and pollen, can be estimated from outdoor aeroallergen networks, local vegetation information, and residence specific information.

I.c. **Sub-Hypotheses: Asthma Severity and Early Markers**

- Exposures to air pollution and aeroallergens exacerbate existing disease. Therefore, the number and severity of asthma attacks in children increases with chronic air pollutant and allergen exposures. In addition, the growth in lung capacity and other pulmonary function measurements is inversely associated with chronic air pollutant and aeroallergen exposures.

- Chronic exposures to air pollution and aeroallergens are positively associated with increased inflammatory markers in the blood, such as immunoglobulin E (IgE) and the interleukins (IL-4, IL-5, IL-6, IL-8, and IL-13) and negatively associated with pulmonary function. These associations are present prior to the onset of asthma.

I.d. **Sub-Hypotheses: Effect Modification**

- Air pollutant exposures enhance the allergen-associated risks of asthma and the effect of pre-existing allergic conditions on asthma incidence and severity.

- The association of air pollution and aeroallergens with asthma will be modified by dietary intake of antioxidants, by housing characteristics, and residence location within a city.

II. **Workgroup:** Exposure to Chemical Agents

III. **Contact Person:** Helen H. Suh, Harvard School of Public Health

IV. **Public Health Significance:** An estimated 3.8 million children under 18 years old have asthma, with even more children having undiagnosed asthma. Asthma appears to develop early in life, with asthma incidence increasing dramatically by approximately 75% between 1980 and 1994. The most significant increases have been found in children under five years of age and in children living in the less affluent, urban communities (Gottlieb et al., 1995; Marder et al., 1992; Gergen et al., 1988; Weiss and Wagener, 1990). The reasons for this increase are unknown, but are thought to be related to chronic exposures to air pollutants and to both indoor and outdoor aeroallergens (Sunyer 2001).

The public health, social, and economic impact of childhood asthma is substantial and noteworthy. Asthma is the most common cause of school absenteeism due to chronic disease; the American Lung Association (2002) estimates that childhood asthma accounted for 10.1 million days missed from school annually. The estimated annual cost of treating asthma in children under 18 years old is $3.2 billion.

To date, much of the epidemiological asthma research has focused on the acute effects of air pollution and aeroallergen exposures and on factors that may trigger asthma attacks. Since the 1950's, researchers have consistently shown that acute air pollution ($PM_{2.5}$ and sulfur dioxide) exacerbates asthma and also may increase its incidence (Schwartz and Dockery, 1992; Pope et al., 2000). Furthermore, children who live near a busy road have been shown to be at increased risk of wheezing, a symptom of asthma (Venn et al., 2001). More recently, researchers have demonstrated associations between wheeze or asthma incidence and both dust mite (Platts-Mills et al., 2001) and cockroach allergens (Finn et al., 2000). Consistent with these findings, the asthma symptoms of adults exposed nasally to both diesel exhaust particles (DEP) and dust mite allergen were significantly worse than when exposures were limited to dust mite allergens alone (Diaz-Sanchez et al., 2000). In addition, much smaller-than-usual amounts of allergen caused symptoms when combined with DEP, which by themselves had no effect (Diaz-Sanchez et al., 2000). These results suggest that the combined effects of allergen and air pollutant exposures may be greater than either alone.

The long-term effect of these air pollutant and allergen exposures on asthma incidence and severity are not well understood. For air pollutants, the chronic asthma studies have

shown increased prevalence of respiratory symptoms for areas with higher air pollutant levels (Sunyer 2001). For example, a national (including 53 urban areas) cross-sectional study evaluated the association of citywide mean concentrations of total suspended particles (TSP), obtained from the U.S. EPA network of population based monitors, and chronic bronchitis in the National Health and Nutrition Examination Survey (NHANES). The difference in TSP between the adjusted means of the upper and lower quartiles was 65 $\mu g/m^3$, and the OR for bronchitis across this range of exposure was 1.6 after adjusting for age, race, sex and smoking (Schwartz 1993). A longitudinal study of 3,914 non-smokers residing in California (The Seventh Day Adventist Study) estimated exposure to PM_{10} using monitoring stations linked to residential address. Statistically significant but small positive associations were observed between PM_{10} and severity of asthma, as well as with development of overall airway obstructive disease, chronic productive cough and increased severity of airway obstructive disease (Abbey et al., 1995).

V. **Justification for Large Prospective Cohort Study**

Results from the acute health studies and the few chronic studies suggests that chronic exposures to both air pollution and aeroallergens increase the incidence and severity of asthma. However, currently available databases are not able to answer directly questions about the effects of chronic aeroallergen exposures on asthma nor are they able to examine the effects of chronic air pollutant and aeroallergen exposures on asthma incidence simultaneously. Clearly, these examinations will require the collection of new data and will be best studied in a large prospective cohort study design, which should include children of different ethnicities living across the United States under varied housing, socioeconomic and geographic conditions. The large sample size will be particularly critical for the success of the study, due to the fact that many factors may affect asthma incidence and its severity. A large sample size will allow factors affecting asthma incidence and progression to be identified and the possible synergistic effects of air pollutant and aeroallergen exposures to be examined. Similarly, a prospective design will also be important to the study success, as it will allow the sensitive time windows for asthma to be determined and methods used to estimate long-term exposures to be validated.

VI. **Scientific Merit**

The scientific outcomes of this hypothesis will be three-fold: (1) to estimate chronic exposures to air pollutants, indoor aeroallergens, and outdoor pollens and fungi, (2) to examine the association between asthma and chronic exposures to air pollutants and aeroallergens and (3) to identify exposure-related factors that may modify the association between chronic exposures and asthma. Examination of each of these outcomes will substantially improve our understanding of asthma incidence, management, and prevention and as a result, has the potential to substantially improve the health of children.

Although previous studies have estimated chronic exposures for a variety of air pollutants and to a lesser extent for indoor and outdoor aeroallergens, no method is commonly

recognized as an accurate or precise estimation method for chronic air pollutant or aeroallergen exposures. In large part, this is due to the fact that estimated chronic exposures have been difficult to validate using actual data, due to the short-term nature of most studies and to their reliance on existing databases that were developed to achieve other objectives. A strategy to estimate and validate cumulative exposure to air pollutants and aeroallergens will be critical to our ability to conduct chronic health studies for asthma.

VII. **Potential for Innovative Research**

The potential for innovative research is high. Methods to better characterize cumulative exposure to air pollutants using GIS regression and statistical smoothing techniques and to aeroallergens using annual sampling, residence information, questionnaires, publicly accessible databases will be evaluated and their efficacy determined. Furthermore, various exposure-related factors that modify the exposure-effect relationship will be identified for asthma.

VIII. **Feasibility**

This research will require environmental sampling in the home and blood samples from the participants (for Sub-Hypothesis I.d.) annually for as many as 18 years. Pilot work and current research efforts may allow for reduced amounts of environmental sampling, as factors affecting chronic exposures to aeroallergen and air pollutants are identified. Properly designed questionnaires may serve as a surrogate for some environmental sampling. Publicly accessible databases, such as AIRS, the aeroallergen network, and the US Census, can be used to obtain pertinent information, thus reducing study costs and effort. The study is feasible and with careful study design, the costs can be kept relatively low. Consideration of information gained by repeated environmental measurements will need to be weighed with costs and participant burden.

Literature Cited

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